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patients have been exposed to cannabidiol in placebo-controlled trials, and the sample size for the analysis of effect modification by clobazam (among other factors) becomes larger, then it may be possible to better define the potential for clobazam use to modify the effect of cannabidiol.

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Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy

TO THE EDITOR: The article by Casey et al. (March 2 issue)¹ and the accompanying editorial by Cooper and Pearce² focus on the consequences of maternal subclinical hypothyroidism for the neurocognitive development of the offspring, which was unaffected by the normalization of thyrotropin levels. We suggest that mothers with subclinical hypothyroidism be treated, independently of the inability of a trial to show negative repercussions in offspring with the withholding of levothyroxine therapy.

Increased morbidity, among persons with hypothyroidism as well as among those with hyperthyroidism, may lead to excess mortality.³ In a 7-year follow-up of more than 200,000 persons, as compared with persons with normal thyrotropin levels, the risk of death increased by a factor of 1.09 for each 6 months that a person had a low (<0.30 mU per liter) thyrotropin level ($P<0.001$) and the risk increased by a factor of 1.03 for each 6 months that a patient had an elevated (>4.00 mU per liter) thyrotropin level ($P<0.001$).⁴ Since the thyrotropin level is tightly genetically regulated,⁵ the exact level at which this risk increases in the individual patient is unknown. Therefore, with regard to the trial conducted by Casey et al., the decision to not treat mothers who have subclinical hypothyroidism, as well as the clinical tolerance of subclinical hyperthyroidism (thyrotropin level <0.30 mU per liter) in many of those treated with levothyroxine, may well cause harm, at least in the long term.

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TO THE EDITOR: Among women in the cohort with subclinical hypothyroidism in the trial reported by Casey et al., randomization called for the exclusion of women who were classified as having overt hypothyroidism. Instead, obstetrical providers were notified of test results. The authors call attention to the difference between their findings in women with subclinical hypothyroidism and the results of our case-control

study in 1999 that focused on overt hypothyroidism (thyrotropin level generally >10 mU per liter).¹ Among the offspring of women with overt hypothyroidism, the average IQ was 7 points lower than among the offspring of control women.¹ An estimated 3 to 5 pregnant women per 1000 have overt hypothyroidism.² Under the assumption that ethical considerations in the present trial precluded the randomization of women with overt hypothyroidism, the dilemma posed is whether the IQ difference observed in 1999 can be confirmed in the absence of randomization. Meanwhile, we believe that available data in women with overt hypothyroidism provide support for screening in pregnancy.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Our primary objective was to determine whether routine screening and treatment of otherwise healthy pregnant women for subclinical thyroid hypofunction would increase offspring IQ. Hegedüs and Brix suggest death as a potential harm in women with untreated subclinical hypothyroidism during pregnancy. However, as highlighted in the references included in their letter, the risk of death that is associated with hypothyroidism is significantly confounded by other coexisting conditions, genetic predisposition, and age at diagnosis. An increased risk of death was identified only among persons with overt hypothyroidism that was diagnosed after the age of 60 years. Excess mortality was also not identified among Danish persons with subclinical hypothyroidism. Finally, a recent study showed no benefit, including lower mortality, among older persons who were treated for subclinical hypothyroidism.¹ We therefore cannot agree that the risk of death among mothers justifies routine screening or treatment for subclinical thyroid

disease during pregnancy. Nevertheless, we agree with Hegedüs and Brix regarding their admonition against overtreatment with levothyroxine, especially during pregnancy.

Haddow and Palomaki point to the results of their 1999 study, which focused on pregnant women with overt hypothyroidism and their offspring.² Treatment of such women during pregnancy is well established and may improve neurocognitive outcomes in offspring, as implied by their original findings. Conversely, there is now convincing evidence that the treatment of subclinical hypothyroidism or hypothyroxinemia during pregnancy does not improve neurocognitive outcomes in offspring. As Haddow and Palomaki suggest, the question of routine thyroid screening during pregnancy now seems to hinge on the potential benefits of detecting the less prevalent diagnosis of overt hypothyroidism. Our trial was not designed to answer this question. However, given that overt hypothyroidism is relatively infrequent during pregnancy, that the diagnosis is frequently not confirmed on repeat testing during pregnancy,³ and that treatment of subclinical thyroid hypofunction as early as the second trimester has not been shown to have a benefit with regard to IQ in offspring, we do not consider universal screening for asymptomatic overt hypothyroidism during pregnancy to be justified. Since an acceptable study of sufficient size to answer the dilemma posed is unlikely to be feasible, we believe that targeted screening during pregnancy remains the best option.

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